REMARKS

Claims 2-5 have been canceled.

Claim 1 has been amended by including the limitations of claim 4, the lower limit of abacavir from claim 6 and the upper limit for abacavir from claim 5.

Claim 6 has been amended to depend from claim 1 as claim 5 has been canceled.

Claim 7 has been amended to include the definition of ED50. Support for this amendment can be found in the Specification on page 7, line 5.

No new matter has been added.

Objections

The Examiner objects to claim 7 for use of the abbreviation "ED50" without first specifying the identity of the entities the abbreviation is intended to represent. Applicant has amended the claim to recite the phrase represented by the abbreviation, thereby overcoming the objection.

Rejections Under 35 USC § 112, second paragraph

The Examiner has rejected claim 8 as indefinite, contending that it is unclear whether the ratio presented is a molar or weight ratio. Applicant has canceled claim 8, thereby making the rejection moot.

Rejections Under 35 USC § 103(a)

The Examiner has rejected claims 1-9 as obvious over Margolis et al (US Patent 6,514,979) in view of Harmenberg et al (US Patent 5, 571,798). The Examiner contends that Margolis teaches the synergistic combination of a guanosine analog, such as abacavir, with inosine monophosphate dehydrogenase inhibitors and pharmaceutical compositions for treating HIV infection. The Examiner acknowledges that Margolis fails to disclose the presence of a nucleoside analog, specifically alovudine, which is structurally close to AZT.

The Examiner tries to fill this void by turning to Harmenberg. The Examiner contends that Harmenberg discloses that AZT and its close structural analog alovudine are used agains AIDS and discloses synergistic effects of alovudine (FLT) in combination with a second nucleoside compound such as 2', 3'-dideoxy guanosine where the synergistic ration of the nucleoside compounds is from 50:1 to 1:50.

The Examiner alleges that it would have been obvious for the skilled artisan to optimize the ratios through routine experimentation. He further alleges that it would have been obvious to combine the Margolis teachings with that of Harmenberg since Harmenberg suggest that there is need for new anti HIV drugs with less toxicity than AZT and the combination of nucleoside compounds with different modes of action in cell culture can cause synergistic effects against HIV. Lastly, the Examiner contends that it is obvious to combine two compositions, each of which is taught to be useful for the same purpose, to form a third composition to be used for the very same purpose. Applicant respectfully traverses.

Applicant first notes that claim 1 has been restricted to combinations with weight ratios of 0.5-5 alovudine:300-800 abacavir. In molar terms this means that the minimum ratio of alovudine to abacavir is 1:51.

Applicant next notes that the Examiner in essence states that Margolis combines abacavir (a guanine nucleoside) with a pyrimidine nucleoside, and Harmenberg combines alovudine (a pyrimidine nucleoside) with a guanine nucleoside. The Examiner then concludes that the skilled person would have been motivated to prepare a pharmaceutical composition comprising a combination of abacavir (a guanine nucleoside) and alovudine (a pyrimidine nucleoside). But, as stated in the accompanying Declaration by Dr. Lotta Vrang, this is not exactly true as a more comprehensive analysis of Harmenberg leads to the conclusion that it does not motivate the combination of alovudine and an alternative guanosine nucleoside.

Dr. Vrang notes that all of the experimental results in Harmenberg are based on the combination of alovudine and the pyrimidine nucleoside zidovudine. While Harmenberg refers to the purine nucleoside ddI, Table 1 of the present application shows the combination of ddI and alovudine is markedly less synergistic than alovudine in combination with abacavir.

Dr. Vrang points out that Harmenberg also stresses, for example at col 3, lines 43-49, that for a synergistic effect, the 3'-fluorinated nucleoside such as alovudine should be administered approximately equimolar with the further nucleoside, with an outside boundary of 1:50 in molar terms. She notes that an equimolar formulation is a significantly different regime from the 0.5 - 5 mg alovudine to 300-800 abacavir now claimed. The upper boundary of the alovudine range (5 mg) and the lower boundary of the abacavir range (300 mg) corresponds to a minimum ratio of 1: 51 in molar terms, based on a molecular weight of alovudine of 244 and abacavir 288.

In Dr. Vrang's opinion, if the skilled artisan were to endeavor to extend the teachings of

Harmenberg to guanosine nucleosides, then even at Harmenberg's extreme limit of 1:50 coming nearest to the presently claimed ranges, the performance of the alovudine/ddG combination as proposed by the Examiner would lead away from the presently claimed combination.

Dr. Vrang investigated whether a synergistic effect could be seen in a combination of alovudine and ddG as indicated in the Harmenberg patent. A study was performed to evaluate the Combination Index value of alovudine and ddG. The ED and CI values were calculated as described in WO2004/002433, using a 1:50 ratio of alovudine and ddG. The results are summarized in the table below.

Combination	Molar ratio	Combination Index		
		50% inhibition	75% inhibition	90% inhibition
alovudine+ddG	1:50	1.14	1.59	2.23

These results show a CI above 1 for all three end points measured, namely EC_{50}, EC_{75} and EC_{90} as compared with the alovudine/abacavir combination in Table 1 which shows a CI well below 1. Based on the results of this study, Dr. Vrang concludes that the skilled practitioner, on reading the Harmenberg patent and carrying out a trial with an alovudine/ddG combination would not be motivated to extend the teachings of Harmenberg to another guanosine nucleoside.

Consequently, because the Harmenberg reference actually teaches away from combining alovudine with abacavir, one skilled in the art would not be motivated to combine Harmenberg with Margolis. As such there is no prima facie case of obviousness and Applicant respectfully requests reconsideration and removal of the rejection.

In view of the above remarks, all the claims remaining in the case as amended are submitted as defining non-obvious, novel patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested.

Pursuant to 37 C.F.R. §§1.17 and 1.136(a), Applicant respectfully petitions for a three (3) month extension of time for filing a response in connection with the present application. The Commissioner is hereby authorized to charge Deposit Account 02-2448 in the amount of $1,020 for the required fee.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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